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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/777,526	02/06/2001	Sudhir Agrawal	HYZ-030CPCN3 (47508.518)	8659

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/777,526	AGRAWAL ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 15-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 15-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Amendment filed April 7, 2003, in Paper No. 15.

Claims 12, 13 and 14 have been canceled. Claims 3, 6, 7, and 11 have been amended. New claims 15-27 are acknowledged.

Claims 1-11 and 15-27 are pending in the instant application.

Specification

Applicant's amendment to insert page 42 between pages 41 and 43 is acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,591,721. This rejection is maintained for the reasons of record set forth in the Office Action filed October 8, 2002 in Paper No. 8.

Applicants argue that the claims of the present invention are not unpatentable over claim 1 of U.S. Patent No. 5,591,721. Applicants contend that the present claims do not embrace the method of claim 1 of U.S. Patent No. 5,591,721 because the oligonucleotide used in the U.S. Patent No. 5,591,721 requires "phosphorothioate internucleoside linkages between every nucleoside", while the claims of the present invention require "at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate,

phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester".

Applicant's arguments have been fully considered, but are not found persuasive because claims 1-11 of the instant invention represent a species of the genus of claim 1 of U.S. Patent No. 5,591,721 ('721). For example, the oligonucleotide of claim 1 of '721 requires "phosphorothioate internucleoside linkages between every nucleoside". The specification of '721 discloses phosphorothioate linkages as alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester (see column 6, lines 15-19). Therefore, the chimeric oligonucleotide with at least one phosphorothioate internucleotide linkage, at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester, and at least one 2-O-alkyl ribonucleotide of claims 1-11 of the instant invention embrace the embodiments of claim 1 of '721.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph because the as filed does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is maintained (*in part*) for the reasons of record set forth in the Office Action filed October 8, 2002 in Paper No. 8.

Applicants argue that claims 1-11 are enabled because the specification teaches on of skill in the art how to make and use the invention. Applicants point out specific pages in the

specification as filed that support Applicants arguments that claims 1-11 are enabled. Applicants' further point out that the specification provides examples indicating that the invention worked as claimed. Applicants also provide two references (Appendix A and B) that corroborate the teachings of the instant specification. To further support Applicants arguments, a Declaration under 37 C.F.R. §1.132 was filed which provides *in vivo* data demonstrating oral administration of an oligonucleotide with two 2'-O-methylribonucleotides a the 5' terminal end and four 2'-O-methylribonucleotides at the 3' terminal end was effective in decreasing tumor mass in nude mice, and therefore, would have been present in intact form in plasma at least six hours following oral administration. The Declaration also provides *in vivo* data indicating that an oligonucleotide with four methylphosphonate linkages at both the 3' and 5' ends exhibit oral bioavailability and was present in intact form in plasma at least six hours following oral administration in nude mice.

Applicant's arguments, references that corroborate the teachings of the instant specification, and Declaration under 37 C.F.R. §1.132 have been fully considered and are found persuasive.

However, Applicants also argue that claims 1-11 are fully enabled the art of nucleic acid therapy is no longer unpredictable and therefore would not represent undue experimentation. Applicants rely on a published manuscript (see Craig et al. Exp. Opin. Ther. Patents, 1997 Vol. 7:1175-1182, Appendix C) to provide utility for using oligonucleotides for the treatment of diseases. Applicants further rely on Craig et al. for disclosing the patentability of antisense technology. Applicants argue that the instant invention is not drawn to methods for designing specific oligonucleotides effective for targeting specific genes. Applicants further argue that nor is Applicants' invention directed to a method for predicting or achieving a particular phenotypic

effect, but rather Applicants' invention is drawn to a method of introducing into a mammal an oligonucleotide possessing certain recited structural features, whereby the oligonucleotide is present in intact form in plasma at least six hours following oral administration. Applicants argue that the effect of the oligonucleotide once it has been introduced intact into the mammal is not an element of the present claims.

Applicants arguments have been fully considered, but are not found persuasive because while the Examiner agrees that the Applicants' invention is drawn to a method of introducing into a mammal an oligonucleotide possessing certain recited structural features, whereby the oligonucleotide is present in intact form in plasma at least six hours following oral administration, as stated in the previous Office Action, there is a high level of unpredictability in the administration of oligonucleotides to whole organisms, such as taught by Branch for administration of antisense oligonucleotides. Branch also teaches that the capacity to deliver genes *in vivo* is requires trial and error experimentation due to unpredictable favors, which include stability of oligonucleotides in the whole organism such that the oligonucleotide may locate and enter a cell and produce the desired effect before degradation. Claims 8-11 specify the oligonucleotide as "complementary to" any gene of a virus, pathogenic organism, or a cellular gene, including those genes involved in the following diseases: AIDS, oral and genital herpes, papilloma warts, influenza, foot and mouth disease, yellow fever, chicken pox, shingles, adult T-cell leukemia, Burkitt's lymphoma, nasopharyngeal carcinoma, hepatitis, Alzheimer's disease, amebiasis, Chagas' disease, toxoplasmosis, pneumocytosis, giardiasis, cryptoporidiosis, trichomoniasis, malaria, ascariasis, filariasis, trichinosis, and schistosomiasis infections. Since a gene targeted for AIDS will not treat Alzheimer's disease, the Examiner disagrees that the instant invention is not drawn to methods for designing specific oligonucleotides effective for

targeting specific genes. Craig et al. at page 1177, last paragraph emphasis that the disease treating specificity of the oligonucleotide is provided by its nucleotide sequence. The Examiner further believes that the effect of the oligonucleotide once it has been introduced intact into the mammal *is* an element of the present claims, since methods of treatment are contemplated in the specification as filed. While Applicants reference of Craig et al. disclose the patentability of antisense technology, this reference does not teach how one of skill in the art would use complementary oligonucleotides of the instant invention to treat any one of the broad range of divergent/unrelated diseases contemplated by the instant specification as filed.

Further, the claimed oligonucleotides "complementary to" the disease genes in claims 8-11 are not supported by teaching in the specification as filed as to specific oligonucleotide sequences which show complementarily to the claimed genes. Specifically, the specification does not teach what sites of the claimed genes as broadly claimed would be available to such complementary application of an oligonucleotide. Further, the lack of teaching of specific conditions in the specification as filed as to the conditions allowing for complementarily of an oligonucleotide to the broad genus of claimed genes lends a great deal of unpredictability to the design and application of such oligonucleotides. Specifically, a great deal of "trial and error" experimentation would necessarily be performed to determine the various conditions for complementary (such as nucleotide sequence, length, etc.) without such guidance in the specification as filed. Therefore, it would require undue experimentation to make and use the invention as claimed.

Information Disclosure Statement

The information disclosure statement filed October 7, 2002 in Paper No. 13 is acknowledged. The Examiner has considered the listing of references in the information disclosure statement.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,591,721 ('721). Although the conflicting claims are not identical, they are not patentably distinct from each other because: The oligonucleotide of claims 15-22 of the instant invention, embrace the oligonucleotide of claim 1 of '721. Claims 15-22 of the instant invention represent a species of the genus of claim 1 of '721. For example, the oligonucleotide of claim 1 of '721 requires "phosphorothioate internucleoside linkages between every nucleoside" and at least two 2'-O-methyl-ribonucleotides at each end. The specification of '721 discloses phosphorothioate

linkages as alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester (see column 6, lines 15-19). Therefore, the chimeric oligonucleotide with at least one phosphorothioate internucleotide linkage, at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester, and at least one 2-O-alkyl ribonucleotide of claims 15-22 of the instant invention embrace the embodiments of claim 1 of '721.

Claims 23-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,591,721. Although the conflicting claims are not identical, they are not patentably distinct from each other because: The oligonucleotide of claims 23-27 of the instant invention, embrace the oligonucleotide of claim 1 of '721. Claims 23-27 of the instant invention represent a species of the genus of claim 1 of '721. For example, the oligonucleotide of claim 1 of '721 requires "phosphorothioate internucleoside linkages between every nucleoside" and at least two 2'-O-methyl-ribonucleotides at each end. The specification of '721 discloses phosphorothioate linkages as alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester (see column 6, lines 15-19). Therefore, the chimeric oligonucleotide with at least one phosphorothioate internucleotide linkage, at least two alkylphosphonate internucleotide linkages at its 3' and 5' terminal ends and at least two 2'-O-alkyl ribonucleotides at its 3' and 5' terminal ends of claims 23-27 of the instant invention embrace the embodiments of claim 1 of '721.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
June 26, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635